



Case report

A methemoglobinemia case who was previously diagnosed and treated as asthma

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ARTICLE INFO

Article history:

Received 17 April 2012

Accepted 8 August 2012

Keywords:

Bronchial asthma

Hypoxemia

Methemoglobinemia

Cyanosis

ABSTRACT

Methemoglobinemia, one of the rare causes of cyanosis and hypoxemia, may occur in congenital and acquired forms. Coexistence of cyanosis and hypoxemia suggests an etiology associated with an underlying cardiac disease firstly, but if any cardiac pathology exists pulmonary diseases are investigated generally. Considering bronchial asthma in a young patient with shortness of breath is usual. On the other hand, evaluating all the signs and symptoms together with laboratory results is important in diagnosis of rare diseases such as methemoglobinemia. In this paper we present a congenital methemoglobinemia case who was treated with bronchodilator therapy for a period of nearly five years because of misdiagnosis of asthma.

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1. Introduction

Methemoglobinemia, a disorder characterized by the presence of high methemoglobin levels in the blood, can occur in congenital and acquired forms. Methemoglobin is an oxidized form of hemoglobin, which has an increased affinity of oxygen and reduced ability to release oxygen to tissues. The oxygen–hemoglobin dissociation curve is therefore shifted to the left. When methemoglobin concentration is elevated in red blood cells, tissue hypoxia may occur. This disorder may present with several symptoms such as cyanosis, dyspnea, headache. Because it is a rare cause of cyanosis and hypoxemia, the diagnosis of methemoglobinemia is oftenly delayed. Another reason of delayed diagnosis is that unless methemoglobin levels above 40%, the disease often remains asymptomatic. The true diagnosis and treatment of methemoglobinemia reduces mortality. In this paper we present a congenital methemoglobinemia case who was treated with bronchodilator therapy for a period of nearly five years because of misdiagnosis of asthma.

2. Case report

20-year-old male patient was admitted to our outpatient clinic of chest diseases with complaints of chest pain, exertional dyspnea and cyanosis. The patient stated that the complaints are present for

4–5 years and using inhaled bronchodilator therapy with a diagnosis of asthma. In physical examination, vital signs of the patient were normal. Cyanosis is present on the hands and lips, and SpO₂ value was measured as 88–90% in room air. PaO₂ was measured as 54 mmHg in arterial blood gas analysis. Upon this we performed chest radiography and pulmonary artery computerized tomography angiography with a prior diagnosis of pulmonary embolism (acute or chronic), but no pulmonary radiologic lesion was found. Subsequently, ecocardiography was performed for investigating the etiology of hypoxemia but any pathology was not found again. Although patients treated with nasal oxygen with a FiO₂ value of 35%, SpO₂ measurements were about 89–90%. When we received a more detailed history from patient it was learned that his big brother also had similar complaints and he had died for this reason. Thereupon, considering the etiology of hypoxemia in this patient may be related with a congenital hematological disease serum methemoglobin level was measured. Serum methemoglobin level of the patient was 40 times higher than normal range. No history of drug use or environmental exposure which may be related with this laboratory disorder was detected. Taking into account the familial history of the patient and no drug use story, the etiology of the methemoglobinemia was evaluated as congenital. The congenital etiology of methemoglobinemia could not be determined due to lack of laboratory facilities. Before starting treatment we investigated Glucose-6-phosphate dehydrogenase deficiency (G6PD) deficiency and found that the patient does not have G6PD. Upon this, the patient was treated with methylene blue and the methemoglobin levels decreased to 8–9%. Finally, the oxygen saturation value of the patient on room air rose to 94–96% and he was discharged.

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3. Discussion

Red blood cells contain 4 hemoglobin chains which are composed of 4 polypeptide chains associated with 4 heme groups. These heme groups contain iron molecules in the reduced or ferrous form (Fe^{2+}). Ferrous form iron can combine with oxygen by sharing an electron, to form oxyhemoglobin. By releasing the oxygen to the tissues, the iron molecule is restored to its original ferrous state. Hemoglobin can accept and transport oxygen only with the ferrous form iron atom. When hemoglobin becomes oxidized and loses an electron, it is converted to the ferric state (Fe^{3+}) which is called methemoglobin. Because methemoglobin lacks the electron that is needed to form a bond with oxygen, it is incapable of oxygen transport. In methemoglobinemia the oxygen delivery to tissues is impaired and also the oxygen hemoglobin dissociation curve shifts to the left.^{1,2} Generally, methemoglobinemia is accepted as an acquired disorder; however, a very small number of congenital cases are also reported in the literature.^{3,4}

Because of the reduced oxygen-carrying capacity of methemoglobin, cyanosis which is unresponsive to oxygen therapy and sometimes fetal tissue hypoxia in severe cases may be seen in methemoglobinemia. When methemoglobin levels are relatively low especially in congenital methemoglobinemia, cyanosis may be observed without cardiopulmonary symptoms and patient may be observed in a relaxed appearance despite the existence of cyanosis. Cyanosis usually occurs from birth in these patients. Cyanosis does not respond to oxygen therapy and its level depends on the amount of methemoglobin.^{1,2} Methemoglobin levels may be 15–30% in untreated patients. It can be resulted with CNS depression in about 20–45%, arrhythmias, shock and coma in 45–55%, death in over 70% of the patients. Methemoglobin level is lower in patients with anemia but this situation may cause hypoxic symptoms. Erythrocyte life is normal and light compensatory erythrocytosis may be seen in these patients. Before using methylene blue in the diagnosis and the treatment of patient, clinician must be sure that the patient does not have glucose-6-phosphate dehydrogenase (G6PD) deficiency. It should be noted that using oxidants such as methylene blue in patients with G6PD deficiency may cause severe hemolytic crisis.^{5,6} There are two forms of methemoglobinemia, congenital and acquired forms. Diaphorase-I deficiency, hemoglobin variants (Hgb H, Hgb M) and G6PD deficiency are major causes of congenital form.¹ Environmental exposure and toxins are acquired causes of the disorder. Nitrates, chlorates, aniline are agents which may lead to methemoglobinemia.⁷

In a retrospective study 138 cases of acquired methemoglobinemia were examined and etiologic agents were found to be dapsone in 42%, benzocaine in 4%, primaquine in 4% of the patients. A known side effect of dapsone therapy is methemoglobinemia during its usage in autoimmune diseases and prophylaxis against *Pneumocystis pneumonia* (PCP) caused by *Pneumocystis jirovecii*. In another study performed on 242 cases of methemoglobinemia related with anesthesia and benzocaine found to be responsible in 60% of the cases.⁸

In our case there was no history of drug use or environmental exposure, and the most significant complaint was shortness of breath induced by exercise. Considering that the patient's brother also died with similar complaints at the age of fifteen, strengthening the idea that methemoglobinemia is congenital in this

patient. The diagnosis and treatment of bronchial asthma by previous physicians, may be explained with insufficient investigation of the complaints, findings and history.

After exposure to fenasetin and sulfanamid a rare disorder, sulfhemoglobinemia, may occur which can be clinically confused with methemoglobinemia. The distinction can be made by non-responsiveness of sulfhemoglobinemia to treatment with methylene blue. Additionally, the definitive diagnosis can be made by spectrometric examination.⁹

Administration of 1–2 mg/kg IV methylene blue and oral vitamin C have great help for the treatment of methemoglobinemia. N-acetylcysteine, cimetidine and ketokanazol are experimental but promising treatments in methemoglobinemia yet. Exchange transfusion is an alternative treatment in patients who are refractory to methylene blue.¹⁰

We met a similar methemoglobinemia case in the literature who was treated as asthma previously. Because cyanosis and shortness of breath complaints were constant despite the asthma therapy, the patient was detected and homozygous type 1b5r deficiency was found in the patient. The authors stated that the patient was freed from unnecessary treatment and the use of unnecessary drugs.¹¹

Existence of dyspnea, hypoxemia and cyanosis in a patient firstly signs heart diseases (atrial septal defect, ventricular septal defect, etc.) and lung diseases (pulmonary embolism, etc.). Therefore evaluation of these diseases is a normal procedure. On the other hand considering methemoglobinemia may be life-saving before making a bronchial asthma diagnosis in such young patients in whom the reason for these findings remains un-explained.

As a result, in young adult patients receiving bronchodilator therapy with diagnosis of bronchitis, methemoglobinemia should be considered as the reason of cyanosis and hypoxemia.

Conflict of interest statement

None declared.

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